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Different meanings of "glomerular tip lesion"

To the Editor: The term "glomerular tip lesion" [1] has been used with three meanings:

(*1*) Our original description was in nephrotic patients with structural changes at the tubular origin in glomeruli that were otherwise normal. The clinical course resembled that of minimal change nephropathy [2].

(*2*) We later realized that such changes were a common finding in many disorders, such as membranous nephropathy [3]. These *tip changes* were not themselves a disease, but could only be interpreted by consideration of the rest of the glomerulus. Others have applied the term "glomerular tip lesion" to these changes, irrespective of the associated condition.

(*3*) We also reported tip changes in glomeruli showing mesangial hypercellularity in the nephrotic syndrome, sometimes with clinical progression [3, 4]. The ones who did badly developed segmental sclerosis, corresponding to many descriptions of "focal segmental glomerulosclerosis." We called the early stage *early classical focal segmental glomerulosclerosis* [4].

'Glomerular tip lesion,' as defined by D'Agati et al [1], also called "the tip variant of focal segmental glomerulosclerosis," clearly includes our original definition, and excludes tip changes in conditions such as membranous nephropathy. Their definition allows mesangial hypercellularity, and some of their patients may correspond to early classical focal segmental glomerulosclerosis. Differentiation between normal mesangium and mild mesangial hypercellularity is arbitrary, but at the moment there is no other satisfactory test to identify those who may progress.

We agree with D'Agati et al that most patients with the "glomerular tip lesion" by their definition, have steroid responsive nephrotic syndrome and a good prognosis.

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Reply from the Authors

We agree with Dr. Howie that glomerular tip lesion (GTL) may occur as a primary form in patients with idiopathic nephrotic syndrome, or may develop secondarily in association with heavy proteinuria in diverse glomerular diseases [1]. We limited our study to primary GTL [2]. In our series, mesangial hypercellularity did not predict outcome, defined as remission status at last follow-up. None of our cases of primary GTL showed more than mild mesangial hypercellularity, which was detected in 47% of GTL biopsies. Notably, the single GTL case that progressed to end-stage renal disease lacked mesangial hypercellularity.

Dr. Howie has observed that those cases with "structural changes at the tubular origin in glomeruli that were otherwise normal" had a "clinical course resembling that of minimal change disease." Our data have shown, for the first time, that routinely processed renal biopsies with GTL frequently contained glomeruli with segmental lesions at other sites (peripheral or indeterminate, but not perihilar), and most of these cases similarly followed a benign course. Importantly, the segmental lesions were predominantly cellular (81%), rather than sclerosing. There was no significant difference in remission status when cases with GTL alone (26% of cases) were compared with cases of GTL with segmental lesions at other glomerular locations. Remission rate for GTL was better than for idiopathic focal segmental sclerosis controls, but not as good as that reported for adult minimal change disease. For these reasons, we envision GTL as occupying an intermediate position, morphologically and clinically, in the minimal change disease/focal segmental glomerulosclerosis spectrum [3].

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How can we be sure that renal dysfunction after coronary angiography is just explained by contrast nephropathy?

To the Editor: A review has been performed on the very hot topic of the role of N-acetylcysteine (NAC) on contrast nephropathy (CN) [1], of great clinical impact as a result of the CN-linked role in worsening prognosis and increasing costs. The authors wrote that they "assess the efficacy of NAC for preventing CN after . . . *intravenous* contrast media," and concluded that "NAC may reduce the incidence of increased creatinine after administration of *intravenous* contrast, but this was of borderline statistical significance." However, both sentences are wrong and misleading, as are similar conclusions reached by another meta-analysis [2], because all 15 [1] or 16 [2] reviewed papers regarded coronary angiography (CA), except one [3]. First of all, to perform CA, contrast media are introduced into the arterial vascular bed, and not intravenously, as when performing computed tomography (CT). Second, mechanisms of renal dysfunction after CA are not only caused by CN, but also by other causes such as, for instance, cholesterol crystal embolization.

We suggest that: (*1*) further studies be analyzed by separating prevention strategies for CT from those for CA; (*2*) for CA, attempts will be made to dissect other causes of renal damage by looking for the blue toes syndrome or eosinophilia, in order to exclude cholesterol embolization; (*3*) even urea increase was considered as end point, to avoid the possibility that creatinine changes might be resulting simply from a direct effect of NAC [4].

The only quoted paper regarding the use of NAC before performing CT did demonstrate a protection, by also using urea values as end point [3].

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Reply from the Authors

We thank Dr. Canavese et al for their letter. We agree that the term "intravenous contrast administration" may have been misleading. Perhaps the term "parenteral contrast administration" would have been preferable.

As we mentioned in our article, atheroemboli might explain why NAC seemed to be less efficacious than computed tomography in the context of coronary angiography. For this reason we performed subgroup analysis including only trials of patients undergoing coronary angiography. Although "looking for blue toes or eosinophilia" has theoretical appeal, we are uncertain how helpful this would be, because such findings may take weeks to appear [1], and clinically silent cholesterol embolization after invasive procedures appears to be common [2].

The suggestion to use serum urea rather than creatinine as an outcome measure seems to miss one of the main points of our article—that data on costs or clinically relevant outcomes such as death or hospitalization (and not surrogates such as estimated kidney function) are needed.

After reading their letter carefully, we are uncertain whether Dr. Canavese et al feel that our conclusions are